New Figures 1 and 4 are submitted herewith in lieu of illegible original Figures 1 and 4. It is believed that the other figures are suitable for examination but may of course be replaced at the time of payment of the issue fee, should the official draftsman so require.

The claims previously in the case have been replaced by a new set of new claims that are believed to be proper as to form and clearly patentable over the cited references.

In the new claims, careful attention is paid to the Examiner's formal objections, all of which are believed to be satisfied by the new claims.

Reconsideration is accordingly respectfully requested, for the rejection of the claims on 35 USC §112 for lack of written description sufficient to indicate that applicants were in possession of the claimed invention at the time of filing of the application.

In this regard, it was considered in the Official Action that the specification does not sufficiently describe "the boundaries for what constitutes the "whole" or the "part" of PLA2s promoter".

This part of the present rejection has been rendered moot since the amended claims no longer recite "whole" or part".

With respect to the term "functional variant" or "functional part" the specification as filed provides clear definitions and recites the essential features for characterizing

the structural and functional properties of a "part" of the PLA2s promoter as well as a "functional variant" of PPAR-binding element encompassed by the claims under consideration.

What is meant by "functional part" of the promoter for the PLA2s gene is indicated at least on page 11, lines 17-21 in the application as filed. An essential feature of these fragments of the sequence is that they conserve biological functionality, i.e., they conserve a basal transcriptional activity for the hybrid promoter and a character regulable by the inflammation mediators.

Furthermore, the specification recites that the "functional part" of the promoter designates any fragment of the sequence having a basal transcriptional activity for the hybrid promoter, for example.

In the specification as filed, applicants describe the promoter of PLA2s gene including in the hybrid promoter as presently claimed. The promoters designated at least on page 11, lines 13-21 are the sequence SEQ ID NO:5 corresponding to nucleotides -247 to +20 of the human gene for PLA2s IIA. Applicants teach SEQ ID NO:5 as ensuring a basal transcriptional activity for the hybrid promoter as described at least on page 11, lines 19-21 and a character regulable by the inflammation mediators. Therefore, as the entire promoter of the human gene for PLA2s IIA is disclosed in the specification, one skilled in the art can test any fragments of the sequence in order to check

their biological functions. In view of the above, a skilled artisan would be adequately instructed by the specification on at least page 31, lines 9-23. Furthermore, a skilled artisan could find in reviews or books forming part of the general knowledge in the field of the invention any other experimental procedures to identify part of the promoter for the PLA2s gene having a basal transcriptional activity.

What is meant by "functional variant" is defined at least on page 7, lines 15-30 of the application as filed. More specifically, it is stated that a functional variant designates any modified sequence conserving the properties of PPRE as mentioned above, that can bind to PPAR. These modifications may be undertaken using conventional methods known in the art such as site-directed mutagenesis. At least page 8, lines 1-9 of the specification describes to the skilled artisan how to test for PPRE activity. Moreover, such a method for assaying the capacity to bind a PPAR forms part of the general knowledge in the field of the invention. A person skilled in the art could easily test modified variants and identify which ones have the capacity to bind a PPAR.

The limitation of a "functional variant" is in fact sufficient to provide a structural/functional basis for one skilled in the art in order to define the broadly claimed genus. Further, the Examiner submits that the number of alternatives for SEQ ID NO:1 comprising 20 nucleotides is 2^5 variants.

Variants were obtained by modifications like additions, mutations, deletions and/or substitutions of nucleotides in the considered sequences. These alternatives of modification may generate different functional variants which are described for example in JUGE-AUBRY et al. (J. Biol. Chem. 272 (1997) 25252) and NAKSHATI et al. (NAR 26 (1998) 2491). Modifications obtained by mutation, for example, have a low frequency of realization; consequently, the number of variants is not high for SEQ ID NO:1 but a lower number of alternatives relating to the modification frequency, which is low. Indeed, variants are nucleotide sequences with a defined number of nucleotides according to SEQ ID NO and consequently these nucleotide sequences have a common structure. Furthermore, the specification discloses the common features and attributes possessed by members of the genus which conserve the properties of PPRE, that is to say the capacity to bind a PPAR.

Reconsideration is also respectfully requested for the rejection of certain of the claims under 35 USC §112, second paragraph, as being indefinite and not distinctly claiming the invention.

Part of this rejection has been obviated by the amendments of claims 1, 2, 3 and 4.

According to this rejection, the term "hybrid promoter" in claim 1 is not defined in the specification. What is meant by "hybrid promoter" is indicated at least on page 4, line 2 and

page 4, line 12 in the specification as filed. These explanations underline that a hybrid promoter is constituted by two distinct promoter regions and is produced by collinear union of two fragments of DNA. Thus, whether the phrase "the whole or part of the promoter of PLA2s gene", as presently claimed, is unclear, has been rendered moot since the amended claims no longer recite "whole" and "part."

The application as filed explains at least on page 10, line 22 to page 11, lines 17-21 the term "functional part" of the PLA2s IIA promoter. "Functional part" designates any fragment of the sequence considered to conserve biological functionality. Furthermore, the description describes that the part of the promoter must ensure basal transcriptional activity and has a character regulable by the inflammation mediators.

In the rejection under 35 USC §112, second paragraph, it was deemed that the term "functional variants" in claims 3 and 4 is not defined in the specification. What is meant by "functional variants" is designated at least on page 7, lines 15-29 in the specification. These variants were obtained by modifications encompassing one or more additions, mutations, deletions and/or substitutions of nucleotides in the sequence. The said variants conserve the properties of PPRE to bind PPAR.

Reconsideration is accordingly respectfully requested, for the rejection of the claims as anticipated by COUTURIER et al., "Interleukin 1β Induces Type II-secreted Phospholipase A_2

Gene in Vascular Smooth Muscle Cells by a Nuclear Factor κB and Peroxisome Proliferator-activated Receptor-mediated Process", J. Biol. Chemistry, August 1999, Vol. 274, No. 33, pp. 23085-23093 or EVANS et al. 6,413,994.

COUTURIER et al. teach the induction of PLA2s gene transciption by the following compounds IL-1β, NFκB and $PPAR_\gamma$. COUTURIER et al. describe particularly in Figure 9B, page 23091, first column, a plasmid construct containing two PPRE consensus regions and a thymidine kinase promoter region fused to a luciferase reporter gene, said construct being used to test the effect of IL-1β on the transcriptional activity. Furthermore COUTURIER et al. observe that PLA2s promoter has an extensive homology with the DR1 element a PPAR-binding site as disclosed at page 23090, column 2. The Official Action indicates that the PLA2s promoter comprises at least one PPAR-binding element with extensive homology with DR1 a PPAR binding element. But just because DR1 element sequence is present in <u>both</u> sequence PLA2s promoter and PPRE does not mean that COUTURIER et al. disclose a hybrid promoter as in claim 26. Thus, in view of the above, COUTURIER et al. fail to teach the construction of a hybrid promoter comprising a PPRE and the promoter of PLA2s gene as presently claimed.

EVANS et al. teach the effect of antagonist or partial-agonist of $PPAR_\gamma$ on the modulation of a nuclear receptor mediated process. This reference describes, particularly in Example 2,

column 12, reporter constructs with three copies of PPRE upstream of the TK promoter fused to luciferase reporter gene (LUC). The Official Action indicates that one nucleotide of the TK promoter would necessarily comprise at least one nucleotide from the PLA2s promoter, but this rejection should be moot since claim 26 has been modified to a functional part. Indeed, the specification of the outstanding application explains that a "part" of PLA2s promoter corresponds to a "functional part" of promoter having a basal transcriptional activity and regulable by inflammatory agents. Consequently, one nucleotide of PLA2s promoter cannot satisfy the above features of a "functional part" of PLA2s promoter. Therefore, in view of the above, EVANS et al. do not disclose the construction of a hybrid promoter comprising a PPRE and the promoter of PLA2s gene.

As the claims now as now constituted clearly bring out these distinctions with ample particularity, it is believed that they are all patentable, and reconsideration and allowance are respectfully requested.

Respectfully submitted,

YOUNG & THOMPSON

By 

Robert J. Patch
Attorney for Applicants
Registration No. 17,355
745 South 23rd Street
Arlington, VA 22202
Telephone: 703/521-2297

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